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*Published in:*  
Seminars in thrombosis and hemostasis

*DOI:*  
[10.1055/s-0037-1603447](https://doi.org/10.1055/s-0037-1603447)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2017

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Bos, S., Bernal, W., Porte, R., & Lisman, T. (2017). Hemostatic Complications in Hepatobiliary Surgery. *Seminars in thrombosis and hemostasis*, 43(7), 732-741. <https://doi.org/10.1055/s-0037-1603447>

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# Hemostatic Complications in Hepatobiliary Surgery

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Semin Thromb Hemost 2017;43:732–741.

## Abstract

Hepatobiliary surgery is a well-known risk factor for thrombotic complications but is also associated with substantial perioperative blood loss. Given the central role of the liver in hemostasis, hepatobiliary surgery is frequently accompanied by complex changes in the hemostatic system. Increasing knowledge of these changes has resulted in an improved understanding of the etiology of some of the hemostatic complications. In the early postoperative period a prolongation of conventional coagulation test times, such as the prothrombin time, is frequently seen. Together with a decreased platelet count, this suggests a hypocoagulable state. The concomitant decline of anticoagulant factors and development of a von Willebrand factor/ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) imbalance, however, suggest a hypercoagulable state, potentially contributing to the risk of thromboembolism. Postoperative thromboprophylaxis should be initiated early to avoid thrombosis, and intensified prophylaxis might benefit high-risk patients. The risk of hemorrhagic complications during hepatobiliary surgery has diminished over time, mainly due to improved surgical and anesthesiological techniques. However, bleeding can still be profound in individual patients and is difficult to predict using (global) hemostasis tests. A restrictive transfusion and fluid infusion policy to maintain a low central venous pressure is crucial in prevention of perioperative bleeding. However, when active bleeding occurs, proactive prohemostatic management is required.

## Keywords

- hepatectomy
- liver transplantation
- pancreatectomy
- thrombosis
- bleeding

Hepatobiliary surgery is associated with a substantial risk of bleeding and thrombotic complications. Given the central role of the liver in hemostasis, it is not surprising that hemostatic changes occur during and after partial hepatectomy or liver transplantation. Also, preoperative hemostatic abnormalities are frequently present in patients with the (end-stage) liver disease.<sup>1</sup> Bleeding during partial hepatect-

omy may be largely due to surgical and anatomical factors, but perioperative changes in the hemostatic system may also contribute.<sup>2,3</sup> During liver transplant surgery, the substantially altered hemostatic system may contribute to bleeding, although surgical and anesthesiological factors and portal hypertension contribute significantly.<sup>4,5</sup> The risk of deep vein thrombosis following hepatobiliary surgery is not negligible,

published online  
June 13, 2017

Issue Theme Thrombosis and Hemostasis in Surgery; Guest Editors: Anne-Mette Hvas, MD, PhD, Julie Brogaard Larsen, MD, and Leonardo Pasalic, PhD, MBBS, FRCPA, FRACP.

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Tel: +1(212) 584-4662.

DOI <https://doi.org/10.1055/s-0037-1603447>.  
ISSN 0094-6176.

even in patients receiving adequate thromboprophylaxis.<sup>6</sup> In liver transplant recipients, thrombotic complications of the hepatic artery or portal vein may occur, and may directly compromise graft function and vitality.<sup>7,8</sup> Prevention and treatment of bleeding and thrombosis, therefore, are essential in the management of patients undergoing hepatobiliary surgery.

In the past decade, clinical and laboratory studies have led to a better understanding of the status of the hemostatic system of the patient undergoing hepatobiliary surgery. These new insights are significant to further optimize clinical management.<sup>9,10</sup>

In this article, we will provide an overview of the new insights in hemostatic changes during hepatobiliary surgery. Also, developments in understanding risk factors and the possible predictors of hemostatic complications during the perioperative period of hepatobiliary surgery will be discussed. Finally, strategies for prevention and treatment of bleeding and thrombotic complications will be summarized.

## Hemostatic Changes during and after Hepatobiliary Surgery

Patients undergoing hepatobiliary surgery may have an intact hemostatic system before the procedure, for example, patients requiring a partial hepatectomy for metastasized colon cancer, or patients with a metabolic disorder requiring liver transplantation. However, frequently the hemostatic function is already substantially compromised, such as patients with cirrhosis requiring partial hepatectomy or liver transplantation. The hemostatic changes of patients with cirrhosis have been reviewed extensively elsewhere.<sup>11–13</sup> In short, despite alterations in routine indices of hemostasis such as the platelet count and the prothrombin time (PT), patients with cirrhosis appear to be in hemostatic balance due to a concomitant decline in pro- and antihemostatic drivers.<sup>13</sup> During hepatobiliary surgery, substantial (additional) changes in the hemostatic system occur. These are likely due to a combination of factors. On the one hand, there is consumption induced by surgical damage and reperfusion injury during liver transplantation, hemodilution, decreased or absent synthesis of liver-derived hemostatic components following partial hepatectomy or during the anhepatic phase of liver transplantation.<sup>14,15</sup> On the other hand, there is a decreased or absent clearance of activated hemostatic proteins when functional liver volume becomes compromised.<sup>14,15</sup> Such changes lead to further abnormalities in routine diagnostic tests of hemostasis. We will summarize new insights into the development of hemostatic abnormalities during partial hepatectomy and liver transplantation below.

### Primary Hemostasis

The platelet count decreases during and after partial hepatectomy and liver transplantation, reaching a nadir around day 3, after which it rapidly increases to supraphysiological levels.<sup>16–18</sup> An imbalance in the von Willebrand factor (VWF)/ADAMTS13 (a disintegrin and metalloproteinase

with a thrombospondin type 1 motif, member 13) axis has been suggested to compensate (in part) for the thrombocytopenia of cirrhosis and acute liver failure.<sup>19,20</sup> A similar mechanism likely acts during and after partial hepatectomy and liver transplantation, as high VWF, low ADAMTS13, and enhanced VWF-dependent *in vitro* platelet adhesion have been observed in plasma samples taken during and after both procedures.<sup>21–23</sup> High levels of VWF likely relate to endothelial cell activation, whereas decreased ADAMTS13 is likely due to a combination of hemodilution, consumption, and decreased hepatic synthesis. The imbalanced VWF/ADAMTS13 axis may not only compensate for the thrombocytopenia during these procedures but may contribute to thrombotic risk.<sup>24</sup> Indeed, imbalanced VWF/ADAMTS13 has been shown to be a risk factor for arterial thrombosis in the general population.<sup>25,26</sup> Interestingly, a VWF/ADAMTS13 imbalance also develops during pancreas resection,<sup>22</sup> although to a lesser extent as compared with the imbalance developing during partial hepatectomy, indicating that the decrease in ADAMTS13 following partial hepatectomy is only partly related to decreased synthetic capacity of the remnant liver.

Although the function of the primary hemostatic system may be much better preserved during hepatobiliary surgery than suggested by the platelet count, the developing thrombocytopenia may affect the outcome. Platelets not only are critical in hemostasis but also appear to play a role in liver injury and regeneration. Animal studies have demonstrated that platelets contribute substantially to liver regeneration following partial hepatectomy,<sup>27–30</sup> although the mechanisms involved are incompletely understood.<sup>31</sup> In humans, it has been demonstrated that a low postoperative platelet count is associated with delayed liver function recovery after partial hepatectomy, which suggests that platelets play a critical role in liver regeneration after hepatectomy also in humans.<sup>16,17,32,33</sup> Also, a recent study in living donor transplant recipients demonstrated that in those recipients that did not receive intraoperative platelet transfusions, the intraoperative platelet count was positively associated with graft regeneration as assessed by graft volume measurements by computed tomography.<sup>34</sup>

### Secondary Hemostasis

During partial hepatectomy and liver transplantation, plasma levels of coagulation factors and inhibitors decrease, which is likely related to a combination of hemodilution, consumption, and defective hepatic synthesis.<sup>35,36</sup> In patients with an uncomplicated postoperative course, nadir levels are reached within 24 hours, and coagulation proteins recover to normal levels in the first postoperative weeks.<sup>37,38</sup> The reduction in levels of procoagulant proteins results in a further prolongation in the PT, which suggests a hypocoagulable state.<sup>38,39</sup> In some samples taken during a liver transplant, the PT even becomes immeasurably high.<sup>39</sup> However, the reduction in procoagulants is accompanied by a reduction in natural anticoagulant proteins.<sup>38,39</sup> As the PT is only sensitive to plasma levels of procoagulant proteins; the test does not assess the net effect of concomitant alterations in levels of pro- and

anticoagulant proteins. In addition, plasma levels of procoagulants appear to recover more quickly as compared with levels of anticoagulant proteins.<sup>40</sup> More advanced hemostatic tests including thrombomodulin-modified thrombin generation or thromboelastography, therefore, indicate normo- to hypercoagulability in these patients, despite prolongations in the PT.<sup>39,41–46</sup> Interestingly, one study has shown that a hypercoagulable TEG (Haemonetics Corp, Massachusetts, United States) as defined by a shortened r-time developed in as much as 30% of patients during the anhepatic phase of liver transplantation.<sup>45</sup>

Plasma fibrinogen levels decrease during partial hepatectomy and liver transplantation,<sup>40,47</sup> and recover over time to supraphysiological levels.<sup>48</sup> In patients with cirrhosis, plasma fibrinogen has both hypo- and hypercoagulable features. Specifically, hypersialation impairs fibrin polymerization and thus delays clot formation.<sup>49</sup> However, the ultimately formed fibrin clot has a decreased permeability as compared with clots generated from healthy individuals.<sup>50</sup> As fibrin clot permeability is considered the “gold standard” of fibrin clot quality, we previously concluded that the fibrin clot of patients with cirrhosis has a net prothrombotic nature.<sup>47,50</sup> During liver transplantation, the permeability of the plasma clot increases and the quality of fibrin clot during transplant becomes substantially impaired.<sup>51</sup> Fibrin clot structure, to our knowledge, has not been studied in samples taken during partial hepatectomy.

### Fibrinolysis

During partial hepatectomy and liver transplantation, plasma levels of liver-derived fibrinolytic proteins (i.e., plasminogen, antiplasmin, thrombin-activatable fibrinolysis inhibitor) decreases, whereas levels of endothelial-derived fibrinolytic proteins (i.e., tissue-type plasminogen activator [tPA] and plasminogen activator inhibitor type 1 [PAI-1]) increases.<sup>36,52</sup> The net effect of the complex changes in the fibrinolytic system during and after hepatobiliary surgery is an intraoperative hyperfibrinolytic status in part of the patients, likely because release of t-PA overwhelms the circulating and acutely released PAI-1.<sup>53,54</sup> Following any surgery, a temporary hypofibrinolytic state occurs due to a temporary elevation of PAI-1 (the postoperative fibrinolytic shutdown).<sup>55</sup> Following partial hepatectomy, one study has shown normalization of plasma fibrinolytic potential at day 1, with a “second wave” of hypofibrinolysis between days 3 and 7.<sup>36</sup> Interestingly, a strikingly similar “two wave” hypofibrinolytic state was observed following pancreas resection, indicating that the sustained hypofibrinolytic state is at least in part unrelated to decreased synthetic function of the liver.<sup>36</sup> Following liver transplantation, plasma fibrinolytic potential slowly normalizes over time.<sup>56</sup> Plasma hypofibrinolysis thus characterizes the early postoperative period of hepatobiliary surgery.

### Summary of Hemostatic Status during and after Hepatobiliary Surgery

► **Table 1** summarizes changes in the hemostatic system during and after partial liver resection and liver transplantation.

Maintained hemostatic balance characterizes the hemostatic function of patients during and after hepatobiliary surgery despite intraoperative decreases in plasma levels of hemostatic proteins, decreasing platelet count, and increasing PT. Intraoperatively, the hemostatic balance has distinct hypo- and hypercoagulable features. Specifically, hypofibrinogenemia and hyperfibrinolysis impair hemostasis and might contribute to bleeding, whereas the VWF/ADAMTS13 imbalance and increased thrombin generation capacity support hemostasis and perhaps contribute to thrombosis. Postoperatively, hepatobiliary surgery is characterized by hypercoagulability, which includes VWF/ADAMTS13 imbalance, enhanced thrombin generating capacity, and sustained hypofibrinolysis.<sup>22,36,38</sup> As all these factors have been shown to form a risk factor for thrombotic events in the general population, it is fair to hypothesize that the hypercoagulable status following hepatobiliary surgery may contribute to postoperative thrombotic events, but formal evidence for this is lacking.

### Hemorrhagic Complications

Bleeding may complicate hepatobiliary surgery. Clinically relevant bleeding rates vary widely between centers, but blood loss requiring blood product transfusion is not uncommon. In a published series from our center, one-third of patients undergoing partial hepatectomy required red blood cell transfusions,<sup>32</sup> and mean red blood cell requirements during liver transplantation were eight units.<sup>57</sup> Although the improvements in surgical and anesthesiological techniques have contributed to a substantial decrease in blood loss and transfusion requirements over time,<sup>4</sup> profound blood loss may occur in individual patients. The main causes of blood loss in hepatobiliary surgery consist of surgical and patient-related factors, which includes altered hemostasis in those patients with the end-stage liver disease.<sup>57</sup> Factors that may contribute to bleeding during partial hepatectomy include the quality of liver tissue to be transected, the method of parenchymal transection, and the central venous pressure.<sup>2,3,58,59</sup> In liver transplantation, factors that may contribute to perioperative blood loss are severity and etiology of liver disease, severity of portal hypertension, nutritional state, concomitant renal failure, length of the cold ischemia time, previous surgical procedures, and the type of surgical technique used (vena cava replacement vs. piggyback technique).<sup>4,60,61</sup>

Although blood loss is manageable in the vast majority of patients by surgical repair and transfusion of blood products, there are multiple reasons to limit blood loss as much as possible. Blood loss and blood product requirements have been dose-dependently linked to adverse outcomes including mortality in patients undergoing partial hepatectomy or liver transplant surgery.<sup>4,62</sup> Although mechanisms that may be involved in deleterious effects of blood product transfusion in patients undergoing hepatobiliary surgery are incompletely understood, they include general transfusion reactions including transfusion-related acute lung injury, which appears more prevalent in patients undergoing

**Table 1** Changes in the hemostatic system before, during, and after partial hepatectomy in noncirrhotic patients and liver transplantation in patients with cirrhotic livers

	Preoperative		Intraoperative		Postoperative	
	Partial hepatectomy	Liver transplantation	Partial hepatectomy	Liver transplantation	Partial hepatectomy	Liver transplantation
Platelet count	Normal	Decreased	Decreased		Following an initial decrease, normalization at day 10–14 with no thrombocytosis	
VWF/ADAMTS13	<ul style="list-style-type: none"> <li>• High VWF</li> <li>• Slightly decreased ADAMTS13</li> </ul>	<ul style="list-style-type: none"> <li>• High VWF</li> <li>• Low ADAMTS13</li> </ul>	<ul style="list-style-type: none"> <li>• VWF no change</li> <li>• ADAMTS13 further decrease</li> </ul>	<ul style="list-style-type: none"> <li>• VWF slight decrease</li> <li>• ADAMTS13 substantial decrease, &lt;5% in some patients</li> </ul>	Day 30: <ul style="list-style-type: none"> <li>• VWF remains elevated</li> <li>• ADAMTS13 decreased</li> </ul>	Day 10: <ul style="list-style-type: none"> <li>• VWF remains elevated</li> <li>• ADAMTS13 decreased</li> </ul>
FVIII	Slightly elevated	Substantially elevated	Slight increase	Slight decrease	Slightly elevated at day 30	Substantially elevated at day 10
Pro- and anticoagulant factors (except FVIII)	Normal	Substantially decreased	Decreased		Normalization at day 30	Normalization at day 10
Pro- and antifibrinolytic factors (except tPA and PAI-1)	Normal	Substantially decreased	Decreased		Normalization at day 30	Normalization at day 10
tPA/PAI-1	Normal	Increased	<ul style="list-style-type: none"> <li>• tPA unknown</li> <li>• PAI-1 high at the end of surgery</li> </ul>	<ul style="list-style-type: none"> <li>• tPA peak during anhepatic and/or reperfusion phases</li> <li>• PAI-1 high at the end of surgery</li> </ul>	Normalization at day 30	Normalization at day 10
Prothrombin time	Normal	Prolonged	Prolonged		Normalization after 5–7 d	
Thrombin generation	Normal	Hypercoagulable	Hypercoagulable	Normo- to hypercoagulable	Sustained hypercoagulability until day 30	Sustained hypercoagulability until day 10
Plasma fibrinolytic potential	Normal	Slight hyperfibrinolysis	Hypofibrinolysis at the end of surgery	Hyperfibrinolysis during anhepatic and reperfusion phases, hypofibrinolysis at the end of surgery	Second peak of hypofibrinolysis at day 3, normalization at day 30	Normalization at day 3–5
Thromboelastography	Normal	Hypo-, normo-, or hypercoagulable, dependent on etiology	Normal	Hypo-, normo-, or hypercoagulable	Increased fib-tem at day 5	Unknown

Abbreviations: ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; FVIII, factor VIII; fib-tem, a Rotem system reagent which assess fibrinogen levels of the fibrin clot; PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator; VWF, von Willebrand factor.<sup>16,19,20,33,35,36,53</sup>

Note: Data in this table are based on the published studies of our laboratory<sup>37,42</sup> and others.<sup>37,42</sup>



hepatobiliary surgery as compared with patients transfused in other contexts.<sup>63</sup> Also, transfusion-associated circulatory overload may contribute to exacerbation of bleeding as it increases portal hypertension.

### Thrombotic Complications

Besides an acquired hypercoagulable state related to hepatobiliary surgery, multiple additional risk factors for postoperative thrombotic events may be present in these patients, including (preoperative) cancer, local vascular abnormalities, local abnormalities in blood flow, presence of indwelling catheters, and prolonged postoperative immobilization.<sup>64,65</sup>

#### Partial Hepatectomy

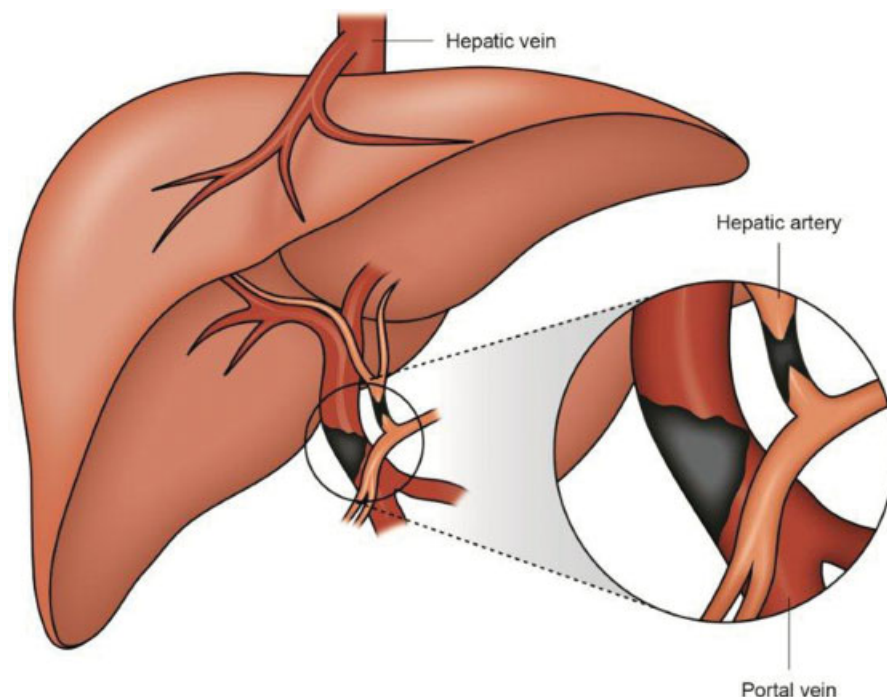
Venous thromboembolism (VTE) occurs after partial hepatectomy, with a reported incidence varying from 2.9 to 4.8%.<sup>6,64–66</sup> In one of the larger retrospective studies, VTE was found to be directly proportional to the magnitude of hepatectomy.<sup>64</sup> Major hepatectomy was associated with a threefold increase in the risk of VTE (1 VTE per 17 patients) compared with minor hepatectomy (1 VTE per 48 patients).<sup>64</sup>

Besides deep vein thrombosis and pulmonary embolism, portal vein thrombosis (PVT, ►Fig. 1) is a frequent complication after hepatectomy, with a reported incidence varying from 2.1 to 9.1%.<sup>67,68</sup> As portal venous flow is an important determinant of liver regeneration,<sup>69–71</sup> it is possible that reduced portal venous flow due to PVT results in delayed liver regeneration.

### Liver Transplantation

Thrombotic events occurring after liver transplantation can be divided into local hepatic vessel thrombosis (►Fig. 1) and systemic thrombotic complications. Hepatic vessel thrombosis poses a threat to both patient and graft survival. The incidence of hepatic artery thrombosis (HAT) is approximately 3 to 7%.<sup>72–75</sup> HAT may occur early (within 2–3 months) after transplantation, but may also occur years after the procedure.<sup>75</sup> Early HAT may result in necrosis of the bile ducts and eventually graft loss if the arterial flow is not restored in time.<sup>73</sup> In comparison with early HAT, late HAT might not be life threatening or even have clinical consequences because of the formation of collateral arterial circulation before total obstruction.<sup>73</sup> Preoperative hypercoagulability, assessed by thromboelastography, has been shown to indicate an increased risk for postoperative HAT.<sup>76</sup> In addition, it has been shown that preoperative PVT is a risk factor for development of postoperative HAT, again suggesting that a relative hypercoagulable state predisposes to HAT.<sup>77</sup>

PVT complicates around 2 to 3.1% of liver transplantations.<sup>7,72,78</sup> Notably, the incidence of preexisting PVT discovered during surgery is considerably higher, 4.9 to 14%, with an even higher incidence in specific subgroups, such as patients with a malignancy.<sup>7,79</sup> The risk of PVT after liver transplantation is related to technical difficulties during surgery, prior PVT, a pediatric recipient, splenectomy, the use of venous conduits, and small portal vein size.<sup>54</sup> Early postoperative PVT can cause acute clinical deterioration because of ischemia, ascites, and increased portal vein pressure.<sup>7,54</sup> Early PVT is associated with an increased



**Fig. 1** Hepatic vessel thrombosis

mortality compared with liver transplant recipients who do not develop a PVT.<sup>8,72</sup>

Systemic thrombotic complications may occur in the perioperative period, but also years after transplantation. Recently, several cohort studies have reported on the overall incidence of VTE after liver transplantation. These reports showed incidences varying between 4.5 and 8.6%.<sup>80–84</sup> Notably, the study that reported an incidence of 8.6% only considered the number of deep vein thrombosis,<sup>82</sup> an even higher incidence would likely have been found if pulmonary embolisms had been taken into account. Importantly, none of the patients in this study received pharmacological thromboprophylaxis.

Although less common, intraoperative thrombosis is of significant relevance due to the association with an increased morbidity and mortality.<sup>45</sup> Intraoperatively, acute intracardiac thrombosis or pulmonary embolism may occur, with an estimated incidence between 0.4 and 6.2%.<sup>85–87</sup> These complications are potentially fatal and appear to be more frequent in liver transplant recipients than in other surgical patients.<sup>88</sup> As previously argued; the current literature shows that a large proportion of the patients undergoing liver transplantation develop a hypercoagulable state during surgery, which may contribute to the development of intraoperative or early postoperative thrombotic complications.<sup>45</sup> Intraoperative hypercoagulability was particularly frequent in patients with cholestatic disease, acute liver failure, and nonalcoholic steatohepatitis.<sup>45</sup>

## Prevention and Treatment of Bleeding

Hepatic resection is often accompanied by intraoperative blood loss primarily occurring during parenchymal transection or tumor resection. Similarly, liver transplantation may also cause excessive blood loss during surgery, which may lead to increased postoperative morbidity and mortality.<sup>89</sup> There are several approaches available to attempt to reduce intraoperative blood loss, as will be outlined below.

Central to our strategy to minimize blood loss is a restrictive fluid infusion policy. Multiple studies have demonstrated that maintenance of a low central venous pressure (CVP) and even a preoperative reduction of CVP by phlebotomy is a beneficial strategy in minimizing blood loss during hepatectomy or liver transplantation.<sup>58,59,90,91</sup> Our fluid restriction management includes the absence of routine prophylactic correction of abnormal coagulation tests (PT or point-of-care). Indeed, routine correction of abnormal coagulation tests with an infusion of fresh frozen plasma (FFP) is not effective in reducing intraoperative blood loss.<sup>5,90</sup> Moreover, preoperative coagulation tests have proven to be very poor predictors of intraoperative bleeding as reviewed in detail by Larsen et al in this issue.<sup>92</sup>

Treatment of bleeding during liver surgery traditionally consists of transfusion of FFP, fibrinogen concentrate or cryoprecipitate, and platelet concentrates guided by routine diagnostic test or point-of-care testing. Transfusion of large amounts of FFP may, in fact, be counterproductive as it leads to fluid overload and a subsequent increase in the central and

portal venous pressure, which is already elevated in many cirrhotic patients. Prothrombin complex concentrate (PCC) may be used as an alternative to FFP. PCC is a low-volume plasma product that contains selected procoagulant proteins and the anticoagulant proteins S and C. The advantage of PCCs over FFP is the low volume and the potential to fully normalize factor levels, while the disadvantage is that PCCs do not contain all procoagulant factors. A recent single-center retrospective study of liver transplant recipients showed that a ROTEM (Tem International GmbH, Munich, Germany)-based approach to administering PCCs and/or fibrinogen concentrate was safe and effective as compared with an FFP/platelet concentrate-based approach.<sup>93</sup> Another low-volume prohemostatic, recombinant factor VIIa (rFVIIa) has been trialed in liver transplantation. A meta-analysis on the use of prophylactic rFVIIa during hepatic surgery, however, did not show efficacy on perioperative bleeding.<sup>94</sup> Although in this meta-analysis rFVIIa did not show an increase in the risk for thromboembolic events, the thrombotic risk is of concern.<sup>94</sup> Position on the use of rFVIIa as a possible rescue agent in patients with intractable bleeding has yet to be defined.<sup>95</sup>

Whereas the evidence for the benefits of blood products in perioperative medicine is low, the supporting evidence for transfusion-related complications including transfusion associated lung injury, transfusion-associated circulatory overload, and infectious complications are increasingly acknowledged.<sup>62</sup> As in other types of surgery,<sup>96,97</sup> transfusion of blood products during liver surgery and liver transplantation has been associated with increased morbidity and mortality.<sup>4</sup> Our current practice is in general one of wait-and-see approach to start blood product transfusion only in actively bleeding patients with evidence of hemostatic abnormalities. Point-of-care testing by thromboelastography is used to guide blood product transfusion.

In the past two decades, improvements in surgical techniques have had an important impact in improving outcome after liver transplantation. Mainly the introduction of the piggyback technique (liver transplantation with preservation of the recipient vena cava) resulted in lower blood transfusion requirements compared with patients transplanted using the 'classical' technique.<sup>98,99</sup>

Although the cause of blood loss during liver transplantation is multifactorial, as noted earlier hyperfibrinolysis has been identified as an important component of the hemostatic dysfunction during this procedure. This has provided a scientific basis for the use of antifibrinolytic drugs, in an attempt to restore the balance between coagulation and fibrinolysis and to reduce blood loss. Tranexamic acid and aprotinin have been shown to reduce blood transfusion requirements by approximately 30% during liver transplantation by well-designed, placebo-controlled, randomized trials.<sup>100–102</sup> No increased risk of thromboembolic complications has been shown in any of the randomized controlled trials.

## Prevention and Treatment of Thrombosis

As the hemostatic system following liver surgery is balanced into a hypercoagulable state, with a corresponding risk of

thrombotic events, a proactive approach to anticoagulant management after liver surgery appears warranted. Importantly, thromboprophylaxis should not be withheld from patients with a prolonged PT or low platelet count, as these factors unjustifiably suggest a hypocoagulable state and increased bleeding risk.

Following partial hepatectomy, pharmacological thromboprophylaxis has been shown to reduce the incidence of postoperative VTE.<sup>6,64,66,103</sup> However, since the risk of thrombotic events, is still appreciable even in those patients receiving optimal thromboprophylaxis, studies on safety and efficacy of more aggressive thromboprophylactic strategies appear warranted. Notably, the current clinical practice appears suboptimal as a recent survey in the United States showed that although the vast majority of hepatobiliary surgeons would use thromboprophylaxis, many would delay heparin administration in patients with thrombocytopenia or a prolonged PT.<sup>104</sup> Also, only 14% of surveyed surgeons would continue prophylaxis after discharge. Nonetheless, awareness of the need for adequate postoperative pharmacologic thromboprophylaxis is increasing, leading to adaptations in clinical guidelines.<sup>105</sup>

Similarly, optimal prevention of thrombotic events following liver transplant surgery requires clinical studies. Whereas we know that a prolonged PT, in this particular study displayed as an increase in international normalized ration (INR), following liver transplantation does not protect from thrombotic disease, it was recently shown that those patients that developed a venous thrombosis following liver transplantation had a significantly higher INR at day 7 after transplantation compared with those that did not develop a thrombotic event.<sup>80</sup> These results suggest that delayed liver function recovery forms a risk for VTE following liver transplantation, and reinforce the notion that thromboprophylaxis should not be withheld from patients with a prolonged PT.

In liver transplantation, there is only one study that reports on the efficacy of pharmacological thromboprophylaxis to prevent systemic thrombosis using subcutaneous unfractionated heparin every 8 hours. The incidence of VTE in the nonheparin group was 3.5 versus 1% in the treated group.<sup>84</sup> In two other cohorts assessing incidence of VTE following liver transplantation, numbers on the use of prophylaxis were absent or only given when patients received anticoagulant treatment before surgery or when an intraoperative thrombectomy was performed.<sup>80,81</sup>

Pharmacological thromboprophylaxis may also help to prevent early PVT or HAT, but to our knowledge, the effect of routine thromboprophylaxis on PVT or HAT has never been assessed in the postliver transplant population. Thromboprophylaxis has been shown to reduce the risk for PVT following partial hepatectomy,<sup>106</sup> suggesting a role for anticoagulation in post-transplant hepatic vessel thrombosis. HAT is traditionally believed to be a surgical complication,<sup>78,107,108</sup> although patient- and graft-related factors such as prior liver transplantation, prolonged cold ischemic time, prolonged operating time, low recipient weight, acute rejection, hemodynamic, infectious and immunological

factors, have also been reported to contribute.<sup>74,76,109</sup> Nevertheless, there is increasing amounts of data suggesting that changes in the hemostatic system may contribute to the development of HAT as well.<sup>54,76</sup> Endothelial damage and activation of the hemostatic system can be the result of cytomegalovirus infection (CMV). Supported by the reported association of CMV with an increased risk of HAT,<sup>109,110</sup> screening, and early thromboprophylaxis and/or antiviral treatment should be considered.

Another possibility in the prevention of HAT is treatment with platelet inhibitors. Two independent studies have shown a significant incidence reduction of HAT by aspirin.<sup>111,112</sup> One of the studies reported a reduction in the overall incidence of HAT from 4.6 to 3.0%,<sup>111</sup> the second study reported an incidence reduction of late HAT from 3.6 to 0.6%.<sup>112</sup> Even though these studies are limited by their retrospective design and study populations are heterogeneous; there was a clear benefit of antiplatelet use without an increase in bleeding events. A further well-designed randomized study to explore safety and efficacy of aspirin to prevent HAT would be indicated. Next, to prophylaxis, early detection of HAT via screening with the regular use of Doppler ultrasound or contrast enhanced ultrasound could be considered.<sup>73,75,78,113</sup>

## Conclusion

Laboratory studies and clinical observations have changed the insights in the hemostatic status during and following hepatobiliary surgery. Whereas conventional hemostasis tests (platelet count, PT/INR) are suggestive of a perioperative-bleeding tendency, more advanced hemostatic tests indicate a balanced hemostasis with hypercoagulable features. The concept of maintenance of hemostatic balance with hypercoagulable features is reflected in the thrombotic risk following liver surgery. Nevertheless, intraoperative bleeding remains a concern, and further refinements in hemostatic management are required to decrease (excessive) blood loss in individual patients. Our management strategies include avoidance of prophylactic correction of abnormal hemostasis tests since they do not predict bleeding events. Blood loss can be minimized through surgical techniques and anesthesiological interventions including a restrictive fluid infusion policy. We advise to use blood products wisely and preferably only when active bleeding occurs. The use of blood products should be guided by conventional hemostasis tests or point-of-care testing, based on the local experience.

Because of a hypercoagulable postoperative state following liver surgery, we suggest initiating pharmacological thromboprophylaxis with low molecular weight heparin as soon as possible. We routinely start thromboprophylaxis at 6 hours after surgery unless active bleeding occurs. It is plausible that a higher dosage of postoperative thromboprophylaxis is needed for specific patient populations with increased risk of thrombotic complications. The prevalence of VTE in hepatobiliary surgery patients, even in those that receive early thromboprophylaxis, stresses the need for further research to optimize thromboprophylaxis in these patients.



## Note

The authors received no financial support, and they have no conflict of interest to disclose.

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